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A rare case of CD5 positive extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) arising in a female breast after surgical excision of an inflammatory pseudotumor

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Summary. Primary lymphoma of the breast is extremely rare accounting for 0.04-0.5% of all breast malignancies. Up to 50% (56-84%) are diffuse large B-cell lymphomas, and indolent histological types such as extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma) occur rarely with a reported incidence variable between 0 and 64%, corresponding to less than 0.5% of overall malignant neoplasms of the breast. A 38-year-old Caucasian woman was admitted to the surgery unit nine months after the excision of a pre-existing inflammatory pseudotumor of the breast because mammography investigation revealed asymmetrical, ill-defined parenchymal accumulation located in the right axillary prolongation. The final diagnosis was obtained after surgical excision and pathological evaluation of the mass. Histological features and the immunohistochemical profile, characterized by positive expression of the lymphoid tumor cells for CD20, BCL-2, and CD5 together with lambda light chain monoclonality and negativity for Cyclin D1, supported the diagnosis of a CD5 positive extranodal marginal zone lymphoma of MALT.

Key words: MALT lymphoma, breast, CD5

«Un raro caso di linfoma del tessuto linfoide associato alla mucosa (MALT Linfoma) della zona marginale extranodale di tipo CD5 positivo, insorgente in mammella femminile dopo asportazione chirurgica di un pseudo tumore infiammatorio»

Riassunto. Il linfoma primitivo della mammella è estremamente raro e presenta una incidenza di 0.04 – 0.5% tra tutti i tumori maligni della mammella. In più del 50% (56-84%) dei casi si tratta di linfomi di tipo B diffusi a grandi cellule, mentre tipi istologici asintomatici come il linfoma extranodale della zona marginale del tessuto linfoide associato alla mucosa (MALT linfoma) sono rari ed hanno una incidenza che varia da 0 a 64%, corrispondenti a meno dello 0.5% di tutte le neoplasie maligne della mammella. Una donna caucasica di 38 anni è afferita all'unità di chirurgia nove mesi dopo l'asportazione di uno pseudo tumore pre-esistente infiammatorio della mammella in quanto l'indagine mammografica aveva rivelato un accumulo parenchimale asimmetrico impreciso localizzato nel prolungamento ascellare destro. La diagnosi finale è stata ottenuta dopo asportazione chirurgica e valutazione patologica della massa. Le caratteristiche istologiche ed il profilo immunoistochimico, caratterizzato dall'espressione positiva delle cellule del tumore linfatico per CD20, BCL-2 e CD5 insieme alla monoclonalità delle catene lambda leggere e insieme alla negatività per Cyclin D1, hanno supportato la diagnosi di un linfoma CD5 positivo della zona marginale extranodale di tipo MALT.

Parole chiave: MALT linfoma, mammella, CD5

Introduction

Primary lymphoma of the breast is extremely rare and it accounts for 0.04-0.5% of all breast malignancies, about 3% of all extranodal lymphomas and approximately 1% of all non-Hodgkin lymphoma (1, 2).

The great majority of primary breast lymphomas are non-Hodgkin's lymphomas (NHL) and are most commonly B-cell subtypes (1). Up to 50% (56-84%) are diffuse large B-cell lymphomas, and indolent histological types such as extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma) occur rarely with a reported incidence variable between 0 and 64%, corresponding to less than 0.5% of overall malignant neoplasms of the breast (1-6). In this report we describe an unusual case of primary CD5 positive MALT lymphoma of the female breast developed after excision of a pre-existing inflammatory pseudotumor at the same anatomical site.

Case report

A 38-year-old Caucasian woman was admitted to the surgery unit of the "G. Martino" Polyclinic (Messina, Italy) in March 2011 after the accidental discovery of a mammary nodular lesion located in the right superolateral quadrant along the axillary line. Ultrasonographic examination confirmed the presence of a diffusely non-homogeneous, both echogenic and hypoechogenic nodular lesion with ill-defined edges (mm 50 at maximum diameter).

Furthermore, in the region of this mass another two nodular lesions were shown: the first was hypoechogenic with well-defined margins (mm 9 at maximum diameter) and the second was non-homogeneous, hypoechogenic and characterized by ill-defined borders (mm 12 at maximum diameter). Total body scintigraphy and CT scan did not reveal the suspected lesions in the cranial, thoracic and abdominal organs. Again, osteomedullary biopsy did not show any pathological alterations. Finally, the patient underwent a wide nodular excision. To a gross examination, the cut surface of the specimen showed a whitish nodular lesion with well-defined edges and increased consistency measuring 19 mm at the greatest dimension. Nine months afterwards, mammography examination revealed asymmetrical, ill-defined parenchymal accumulation located in the right axillary prolongation. The patient accordingly underwent excision of the newly discovered lesion, which to a gross examination consisted of a well-circumscribed whitish nodular mass with sharp margins and firm consistency, measuring 25 mm at the greatest diameter.

Materials and methods

The specimens were fixed in 4% formaldehyde for 24 hours, completely sampled, routinely processed and paraffin-embedded at 56°C. Four micron thick sections were cut and routinely stained with hematoxylin and eosin. Immunohistochemical stainings were performed using commercially obtained antibodies against: CD5 (clone CD5/54/F6; 1:50 working dilution - w.d.; DakoCytomation, Copenhaghen, Denmark), CD3 (clone F7.2.38; 1:100 w.d.; DakoCytomation, Copenhaghen, Denmark), CD20 (clone L26;1:400 w.d.; DakoCytomation, Copenhaghen, Denmark), CD15 (clone C3D-1;1:50 w.d.; DakoCytomation, Copenhaghen, Denmark), CD30 (clone BER-H2;1:40 w.d.; DakoCytomation, Copenhaghen, Denmark), CD10 (clone 56C6; 1:80 w.d. Novocastra Laboratories, New Castle, United Kingdom), CD138 (clone MI15; 1:50 w.d; DakoCytomation, Copenhaghen, Denmark), BCL-2(clone 124; 1:100 w.d.; DakoCytomation, Copenhaghen, Denmark), BCL-6 (clone PGB6P; 1:20 w.d.; DakoCytomation, Copenhaghen, Denmark), Kappa chain (1:50000 w.d.; DakoCytomation, Copenhaghen, Denmark), lambda chain (1:50000 w.d.; DakoCytomation, Copenhaghen, Denmark) and Ki-67 (clone MIB-1; 1:100 w.d; DakoCytomation, Copenhaghen, Denmark).

Results

Histologically, the first lesion observed displayed a nodular proliferation of not atypical small mature-appearing lymphoid cells, devoid of any connective capsule, with clearly evident hyperplastic-typical

CD10-positive germinal centers circumscribed by a mantle zone, which were immunoreactive for CD20. The perifollicular mantle cells immunoexpressed Bcl-2. There were interfollicular CD3 positive lymphoid T cells. Furthermore, Kappa and lambda light chain monoclonality was absent. At the same time, immunostainings for CD5, CD15, CD30 and Bcl-6 were all negative. The conclusive diagnosis was of breast inflammatory pseudo-tumor.

On the other hand, the second pathologic lesion sited in the axillary prolongation revealed a diffuse proliferation of small to medium size lymphoid elements with cleaved centrocyte-like nuclei and moderate eosinophilic cytoplasmatic amount commingled with scattered rate of blasts in the form of centroblastic-like cells and immunoblasts (figures 1A and 1B).

Residual typical germinal centers were likewise visible. The immunohistochemical profile highlighted a diffuse marked positivity for CD20 (Figure 2), CD5 (Figure 3), and BCL-2 but negativity for CD15, CD30, and Cyclin D1. Lambda light chain monoclonality (Figure 4) was apparent in contrast to negative staining for the Kappa counterpart (Figure 5), together with a plentiful background of CD3 positive T-lymphocytes.

CD10 and BCL-6 staining groups of lymphoid cells were encircled by the previously described neoplastic infiltrate that derived from residual germinal centers. Negativity for CD138 confirmed the absence of any plasmacellular differentiation. CKAE1/AE3 immunostain did not reveal any lymphoepithelial lesions within the neoplastic mass. The labeling index with Ki67 was evident in >30% of the neoplastic cells. Hence, the final diagnosis was of extra-nodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) with a large amount of T-lymphocytes. The immunohistochemical results are summarized in Table 1.

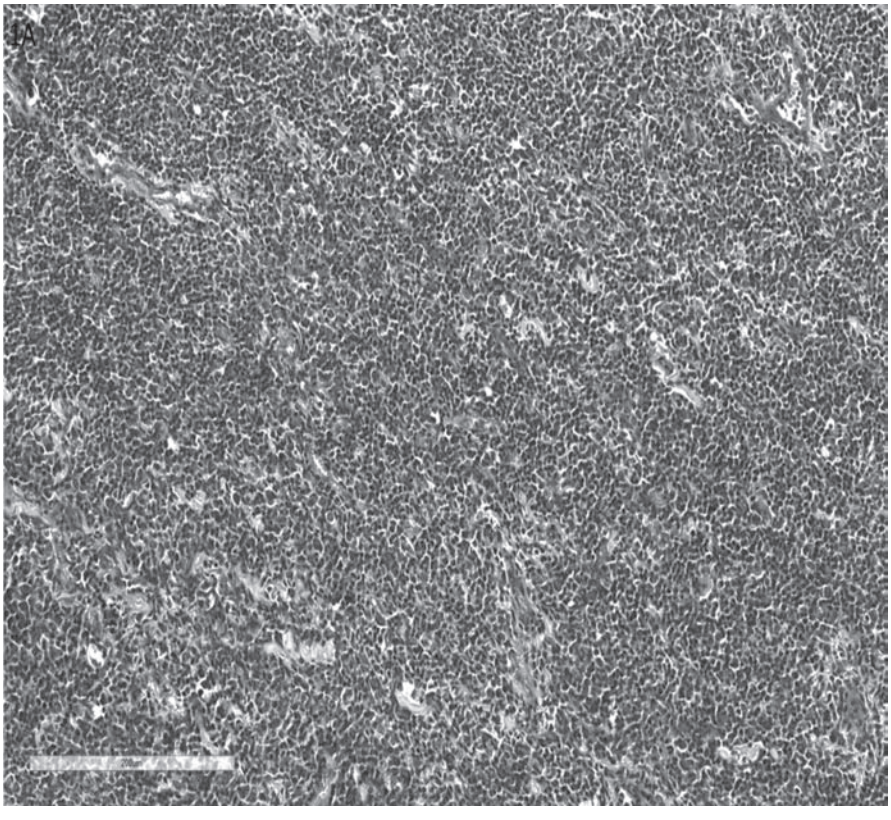

Figure 1A. The tumour showing a diffuse proliferation of small to medium size lymphoid elements, Haematoxylin-Eosin stain, magnification x20

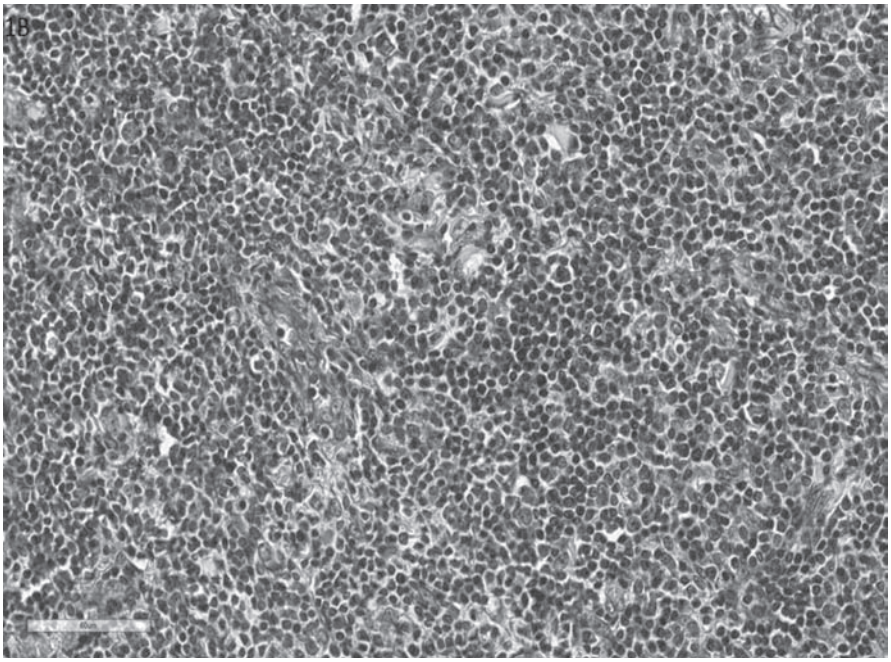

Figure 1B. At higher magnification, centrocyte-like cells commingled with a scattered rate of centroblastic-like cells and immunoblasts are well appreciable, Haematoxylin-Eosin stain, magnification x40

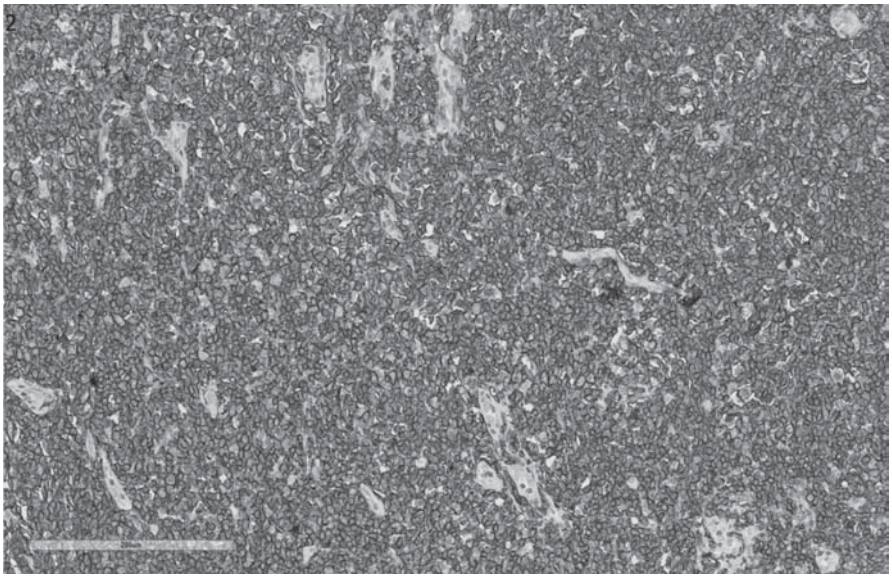

Figure 2. The tumour cells were diffusely and strongly reactive for CD20 immunostain, Mayer's haemalum counterstain, magnification x20

Discussion

According to the definition formulated by the WHO in 2008, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) presents the following characteristics: origin from the marginal zone of the follicles; a heterogeneous lymphoid population in the form of marginal zone (centrocyte-like) cells; an infiltrative pattern that destroys the glandular epithelium forming so-called lymphoepithelial lesions, although detection of these pathological structures is not a dogmatic finding for correct diagnosis of MALT lymphoma (6-8). The etiology of MALT lymphoma is often associated with chronic inflammation forming extranodal lymphoid tissue that is caused by infectious, autoimmune or

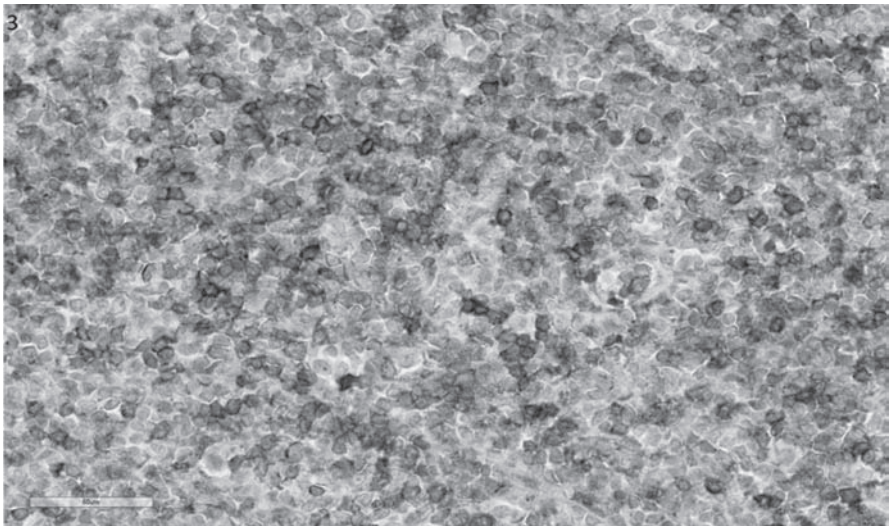

Figure 3. CD5 revealed an evident immunostaining of lymphoid neoplastic cells, CD5 immunostain, Mayer's haemalum counterstain, magnification x40

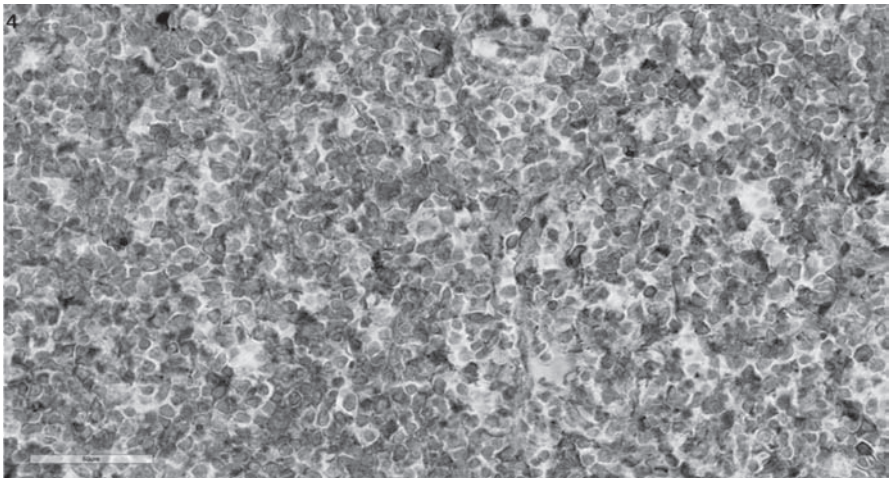

Figure 4. Positive lambda light chain immunostaining, Mayer's haemalum counterstain, magnification x 40

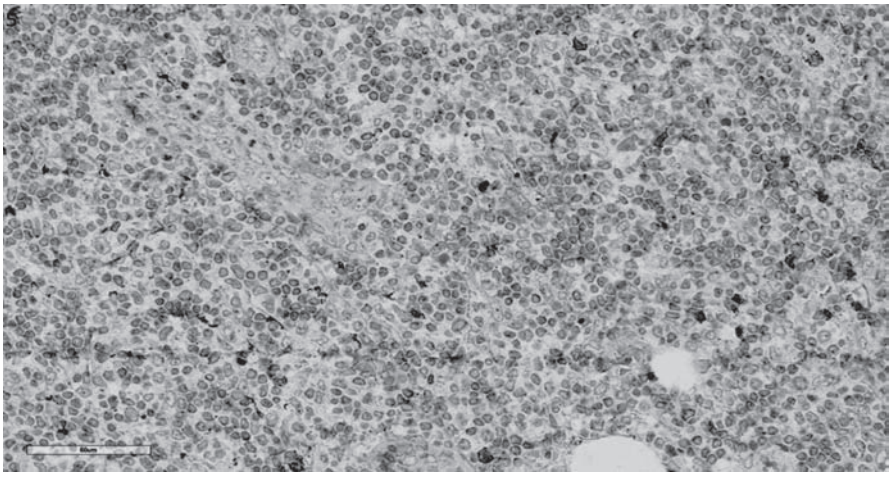

Figure 5. Negative kappa light chain immunostaining, Mayer's haemalum counterstain, magnification x40

Table 1. Immunophenotype of the MALT lymphoma

Antibody	Staining
CD3	-
CD5	+
CD10	-
CD15	-
CD20	+
CD30	-
CD138	-
BCL2	+
BCL6	-
Lambda chain	+
Kappa chain	-
CK AE1/AE3	-
Ki67	>30%

+ positive staining; - negative staining

other unknown disorders (9-10). Specifically for the breast, MALT lymphoma lymphocytic mastopathy characterized by a lymphocytic infiltrate within the glandular epithelium has been reported in association with the development of this lymphoma although its link as a precursor lesion of MALT-type lymphoma of the breast has still not been clarified (10).

Nowadays the MALT lymphoma immunoprofile is characterized by a positive expression of CD20, CD79a, BCL-2, CD43, CD21 and CD35, the latter two being attributable to marginal zone cell-associated antigens (6, 8). On the other hand, CD5, CD10, BCL6, cyclin D1 and CD23 are not immunoreactive, while CD11 staining may be positive or negative (6, 8). However, negative staining for CD5 is not an absolute finding, since it has occasionally been revealed in some MALT lymphomas at various anatomical sites (8, 11-13); this immunoreactivity has been related to a greater tendency to progression and systemic dissemination of lymphomas compared to CD5 negative case (11, 14). Moreover, the evidence of kappa or lambda immnunoglobulin light chain restriction appears to be relevant in the differential diagnosis between MALT lymphoma and benign lymphoid infiltrates (8, 12, 15, 16). Another intriguing point is the differential diagnosis from other small B-cell lymphomas such as mantle cell, small lymphocytic, and follicular lymphoma (8). Thus, in small lymphocytic lymphomas one detects proliferation centers formed of prolymphocytes, small to medium lymphoid cells with clumped chromatin and small nucleoli, and paraimmunoblasts, larger cells than prolymphocytes having round to oval nuclei, dispersed chromatin, central eosinophilic nucleoli and basophilic cytoplasm (17). Follicular lymphomas show: neoplastic follicles enclosed by reduced or absent mantle zone, absence of centroblasts and centrocyte polarization in germinal centers, as well as germinal centers devoid of tangible body macrophages (18). Finally, mantle cell lymphomas lack centroblasts, paraimmunoblasts and proliferation centers (19). Together with routine morphological pictures, the absence of immunoreactivity for certain immunomarkers may in turn be helpful: in the case, for instance, of cyclin D1 this excludes mantle cell lymphoma, while negativity for CD5 differentiates most mantle cell and small lymphocytic lymphomas and, finally, the lack of CD10 distinguishes many follicular lymphomas (8).

Clinically, breast lymphomas manifest mainly in older woman (median age 68 years) as a unilateral solitary mass that mimics a carcinomatous lesion (2, 6, 10). In the literature several cases of primary MALT lymphoma associated with invasive breast carcinoma have been reported, emphasizing the importance of correct distinction between two tumoral entities characterized by different therapeutic approaches as well as prognostic courses (20). In particular, the authors stress the importance of distinguishing MALT-type lymphoma from breast medullary carcinoma characterized by massive lymphoid infiltration, and especially from lobular carcinoma, with its cellular component mimicking plasma cells, which may be a component of MALT lymphoma (20). From a prognostic point of view, primary breast MALT-type lymphomas have an indolent course and a 5-year overall survival of over 90% and a 5-year progression free survival equal to 56% (2, 6). Regarding the therapeutic approach the suggestion is to use surgical excision or radiotherapy for MALT lymphomas in stages IE and II whilst chemo-and radiotherapy is the choice for those in stage III and IV (5, 21).

Cases of "pseudolymphoma" in the breast are rarely reported in the scientific literature (22, 23); they are conjecturally associated with local injuries such as medications, contact allergens, post-zoster scars, arthropod bites, vaccinations, tattoos and infections that

include Borrelia burgdorferi and Leishmania donovani (22, 24). The first nodular lesion observed in the present patient may be attributed to pseudolymphoma, taking into account not only the cytological appearance but also the immunohistochemical profile. However, although breast pseudolymphoma has been considered a benign lymphoproliferative disorder, some experts classify it as very low grade lymphoma since there have been reports of both a progression to overt lymphoma and monoclonality in some cases (16, 22, 23). However, the gold standard for correct diagnosis between malignant lymphoma and pseudolymphoma remains demonstration of the kappa or lambda light chain restriction (12, 15, 16). In the present case, the diagnosis of MALT lymphoma of the breast in the second nodular lesion was warranted by histopathological findings and the immunohistochemical profile which showed immunoglobulin light chain restriction, suggesting progression from a benign disease to malignancy. Moreover, the peculiarity of this newly occurring breast MALT lymphoma was the uncommon CD5 immunostaining in neoplastic cells, suggesting a diagnostic hypothesis of mantle cell lymphoma, which was then ruled out by the immunonegativity for cyclin D1.

In conclusion, in this report we describe the rare transformation of a pseudolymphoma occurring in a female breast toward a lymphoma. In particular, the clinical history, and the microscopy findings, together with the immunohistochemical profile, might support the evolution of an inflammatory pseudo-tumor into a malignant lymphoid proliferation in the form of primary MALT lymphoma rich in T-lymphocytes and with unusual CD5 staining of neoplastic cells.

References

1. Rock K, Rangaswamy G, O'Sullivan S, *et al.* An Unusual Case of Marginal Zone B-Cell Lymphoma Arising in the Breast – Its Diagnosis and the Role of Radiotherapy in its Management Breast Care 2011; 6: 391-3.
2. Cheah CY, Campbell BA, Seymour JF. Primary breast lymphoma. Cancer Treat Rev 2014; 40: 900-8.
3. Maounis N, Ellina E, Papadaki T, *et al.* Bilateral primary lymphoma of the breast: a case report initially diagnosed by FNAC. Diagn Cytopathol 2005; 32: 114-8.
4. Julen O, Dellacasa I, Pelte MF, *et al.* Primary breast lymphomas. Rare Tumors 2009; 22; 1(1): e14.
5. Avenia N, Sanguinetti A, Cirocchi R, *et al.* Primary breast lymphomas: a multicentric experience. World J Surg Oncol 2010; 8: 53.
6. Dogan A, Fend F. Extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma). In: Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijer MJ (Eds.): WHO Classification of Tumours of the Breast, Lyon, France: IARC; 2012:159.
7. Isaacson PG, Du MQ. MALT lymphoma: from morphology to molecules. Nat Rev Cancer 2004; 4: 644-53.
8. Isaacson PG, Chott A, Nakamura S, *et al.* Extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma) . In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J , Vardiman JW (Eds.): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Lyon, France: IARC; 2008: 214-7.
9. Kambouchner M, Godmer P, Guillevin L, *et al.* Low grade marginal zone B cell lymphoma of the breast associated with localised amyloidosis and corpora amylacea in a woman with long standing primary Sjogren's syndrome. J Clin Pathol 2003; 56: 74-7.
10. Taeda Y, Arig N, Okamura K, *et al.* Primary Breast Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma with High-Grade Transformation Evidenced by Prominent Lymphoepithelial Lesions. Breast Cancer 2006; 13 (3): 322-7.
11. Jaso J, Chen L, Li S, *et al.* CD5-positive mucosa-associated lymphoid tissue (MALT) lymphoma: a clinicopathologic study of 14 cases. Hum Pathol 2012; 43: 1436-43.
12. Terada T. CD5-positive marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) of the lung. Diagn Pathol 2012; 7: 16.
13. Mulay K, Honavar SG. Lacrimal gland CD5-positive, primary, extra-nodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT) - Type. Saudi J Ophthalmol 2014; 28: 338-40.
14. Wenzel C, Dieckmann K, Fiebiger W, *et al.* CD5 expression in a lymphoma of the mucosa-associated lymphoid tissue (MALT)-type as a marker for early dissemination and aggressive clinical behaviour. Leuk Lymphoma 2001; 42: 823-9.
15. Kerl H, Fink-Puches R, Cerroni L. Diagnostic criteria of primary cutaneous B-cell lymphomas and pseudolymphomas. Keio J Med 2001; 50: 269-73.
16. Fernandez-Flores A. Cutaneous MALT-lymphoma: from cutaneous immunocytoma and pseudolymphoma to the current (and future) conceptions. Rom J Morphol Embryol 2013; 54: 7-12,
17. Müller-Hermelink HK, Montserrat E, Catovsky D, *et al.* Chronic lymphocytic leukaemia/small lymphocytic lymphoma. In: Swerdlow SH, Campo E,Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J , Vardiman JW (Eds.): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Lyon, France: IARC; 2008: 180-1.
18. Harris NL, Swerdlow SH, Jaffe ES, *et al.* Follicular lym-

phoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J , Vardiman JW (Eds.): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Lyon, France: IARC; 2008: 220.
19. Swerdlow SH, Campo E, Seto M, *et al.* Mantle cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J , Vardiman JW. (Eds.): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Lyon, France: IARC; 2008: 229.
20. Matsuda I, Watanabe T, Enomoto Y, *et al.* Spontaneous regression of primary extranodal marginal zone lymphoma of mucosa- associated lymphoid tissue (MALT lymphoma) colliding with invasive ductal carcinoma of the breast: a case report. Int J Clin Exp Pathol 2014; 7: 7020-7.
21. Martinelli G, Ryan G, Seymour JF, *et al.* Primary follicular and marginal-zone lymphoma of the breast: clinical features, prognostic factors and outcome: a study by the International Extranodal Lymphoma Study Group. Ann Oncol 2009; 20: 1993-9.
22. Maldonado ME, Sierra RD. Pseudolymphoma of the breast: case report and literature review. Mil Med 1994; 159: 469-71.
23. Pecorari P, Rizzardi C, Melato M. Cutaneous pseudolymphoma of the breast with late homozonal relapse. Oncol Rep 2001; 8: 913-5.
24. Hasan M, Shahid M, Varshney M, *et al.* Idiopathic lymphocytoma cutis: a diagnostic dilemma. BMJ Case Reports 2011; doi:10.1136/bcr.12.2010.3662

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